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BIOASSAY OF SODIUM DIETHYLDITHIOCARBAMATE FOR POSSIBLE CARCINOGENICITY

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Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
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Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
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FOREWORD: This report presents the results of the bioassay of sodium diethyldithiocarbamate conducted for the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), National Institutes of Health, Bethesda, Maryland. This is one of a series of experiments designed to determine whether selected chemicals have the capacity to produce cancer in animals. A negative result, in which the test animals do not have a greater incidence of cancer than control animals, does not necessarily mean that a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of circumstances. A positive result demonstrates that a test chemical is carcinogenic for animals under the conditions of the test and indicates that exposure to the chemical is a potential risk to man. The actual determination of the risk to man from chemicals found to be carcinogenic in animals requires a wider analysis.

CONTRIBUTORS: This bioassay of sodium diethyldithiocarbamate was conducted by the NCI Frederick Cancer Research Center (FCRC) (1), Frederick, Maryland, operated for NCI (2) by Litton Bionetics, Inc.

The manager of the bioassay at FCRC was Dr. B. Ulland, the toxicologist was Dr. E. Gordon, and Drs. R. Cardy and D. Creasia compiled the data. Ms. S. Toms was responsible for management of data, Mr. D. Cameron for management of histopathology, Mr. L. Callahan for management of the computer branch, and Mr. R. Cypher for management of the facilities. Mr. A. Butler performed the computer services. Mr. J. W. Warner compiled the data. Histopathologic evaluations for rats were performed by Dr. J. F. Hardisty (3), and the histopathologic evaluations for mice were performed by Dr. C. E. Gilmore (3).

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute (4). Statistical analyses were performed by Dr. J. R. Joiner (5) and Ms. P. L. Yong (5), using methods selected for the bioassay program by Dr. J. J. Gart (6).

The chemicals used in this bioassay were analyzed at FCRC by Dr. W. Zielinsky, and the chemical analyses were reviewed and approved by Dr. W. Lijinsky.

This report was prepared at Tracor Jitco (5) under the direction of NCI. Those responsible for the report at Tracor Jitco were Dr. C. R. Angel, Acting Director of the Bioassay Program; Dr. S. S. Olin, Deputy Director for Science; Dr. J. F. Robens, toxicologist; Dr. R. L. Schueler, pathologist; Dr. G. L. Miller, Ms. L. A. Owen, Ms. M. S. King, and Mr. W. D. Reichardt, bioscience writers; and Dr. E. W. Gunberg, technical editor, assisted by Ms. Y. E. Presley. P. J. Graboske.

The following scientists at NCI were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. Kenneth C. Chu, Dr. Cipriano Cueto, Jr., Dr. J. Fielding Douglas, Dr. Richard A. Griesemer, Dr. Thomas E. Hamm, Dr. William V. Hartwell, Dr. Morton H. Levitt, Dr. Harry A. Milman, Dr. Thomas W. Orme, Dr. A. R. Patel, Dr. Sherman F. Stinson, Dr. Jerrold M. Ward, and Dr. Carrie E. Whitmire.

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SUMMARY

A bioassay of sodium diethyldithiocarbamate for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and B6C3F1 mice.

Groups of 50 rats of each sex were administered sodium diethyldithiocarbamate at one of two doses, either 1,250 or 2,500 ppm, for 104 weeks. Groups of 50 mice of each sex were administered sodium diethyldithiocarbamate at one of two doses, either 500 or 4,000 ppm, for 108 or 109 weeks. Matched controls consisted of 16 untreated male rats, 20 untreated female rats, and 20 untreated mice of each sex. All surviving rats and mice were killed at the end of administration of the test chemical.

Mean body weights of all dosed groups of rats and mice were lower than those of corresponding controls and were dose related throughout the bioassay except those of the low-dose male rats, which were essentially unaffected by administration of the test chemical. Survivals of the rats and mice were unaffected, and no other clinical signs could be related to administration of the test chemical; thus, the animals may have been able to tolerate higher doses. Sufficient numbers of dosed and control animals of each species and sex were at risk for the development of late-appearing tumors.

No tumors occurred in the rats or mice of either sex at incidences that were significantly higher in the dosed groups than in the control groups.

It is concluded that under the conditions of this bioassay, sodium diethyldithiocarbamate was not carcinogenic for F344 rats or B6C3F1 mice of either sex.

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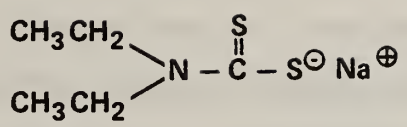
I. INTRODUCTION

Sodium diethyldithiocarbamate (CAS 148-18-5; NCI C02835), is a chelating agent used primarily in the analytical determination of copper, arsenic, nickel, and other metals (Noller, 1966; Thorn and Ludwig, 1962). Other applications include the detection of toxic metals in urine (Kubasik and Volosin, 1973; Vigier et al., 1974), and in the treatment of human poisoning with metals (Thienes and Haley, 1972; Sunderman and Sunderman, 1958).



Sodium diethyldithiocarbamate

Sodium diethyldithiocarbamate has been identified as a metabolite of disulfiram (Antabuse®) (Strömme, 1965), which is used in the treatment of chronic alcoholism (Ritchie, 1975). (For the results of a bioassay of tetraethylthiuram disulfide (disulfiram), see Technical Report 166 of the Carcinogenesis Testing Program, NCI.) The zinc, selenium, and tellurium salts of diethyldithiocarbamate, marketed as ethyl zimate, ethyl selenac, and ethyl tellurac, respectively, are used as fast-acting accelerators in rubber processing (Shaver, 1966).

The LD_{50} of sodium diethyldithiocarbamate in rats when administered by intraperitoneal injection is 1,500 mg/kg (West and Sunderman, 1958). Sodium diethyldithiocarbamate was tested by Innes et al. (1969) in a large-scale screen of industrial compounds for carcinogenic activity. Since the results of this preliminary bioassay in mice did not clearly associate the incidence of any tumor with administration of the test chemical, sodium diethyldithiocarbamate was selected for further testing in the Carcinogenesis Testing Program.

II. MATERIALS AND METHODS

A. Chemical

Sodium diethyldithiocarbamate was obtained as the trihydrate from Matheson Coleman and Bell Company in the form of a yellow-white, fine solid. The effluent from high-pressure liquid chromatography (HPLC) contained two components of which 95% was sodium diethyldithiocarbamate. Its melting point was 91 to 92°C for the anhydrous compound (literature: 94 to 96°C). Elemental analysis of sodium diethyldithiocarbamate $\cdot 3H_2O$ showed an average of 26.6% carbon, 7.3% hydrogen, and 6.4% nitrogen (theoretical: 26.7% C, 7.1% H, and 6.2% N).

B. Dietary Preparation

Test diets containing sodium diethyldithiocarbamate were prepared fresh every 1 to 1-1/2 weeks in 6- to 12-kg batches at the appropriate doses. A known weight of the chemical was first mixed with an equal weight of autoclaved Wayne® Sterilizable Lab Meal with 4% fat (Allied Mills, Inc., Chicago, Ill.), using a mortar and pestle. The mixing was continued with second and

third additions of feed, and final mixing was performed with the remaining quantity of feed for a minimum of 15 minutes in a Patterson-Kelly twin-shell blender. The diets were routinely stored at 5°C until used.

C. Animals

Male and female F344 (Fischer) rats and B6C3F1 mice were obtained as 4-week-old weanlings, all within 3 days of the same age, from the NCI Frederick Cancer Research Center animal farm (Frederick, Md.). The animals were housed within the test facility for 2 weeks and were then assigned four rats to a cage and five mice to a cage on a weight basis for each cage of animals of a given species and sex. Initial weights of male rats used in the chronic study were 90 to 105 g, averaging at least 100 g; of female rats, 80 to 95 g, averaging at least 90 g; of male mice, 18 to 22 g, averaging at least 19.5 g; and of female mice, 17 to 21 g, averaging at least 18.5 g. Individual animals were identified by ear punch.

D. Animal Maintenance

The animals were housed in polycarbonate cages (Lab Products Inc., Garfield, N.J.), 19 x 10-1/2 x 8 inches for the rats and 11-1/2 x 7-1/2 x 5 inches for the mice. The cages were suspended from aluminum racks (Scientific Cages, Inc., Bryan, Tex.) and were covered by nonwoven polyester-fiber 12-mil-thick filter paper (Hoeltge, Inc., Cincinnati, Ohio). The bedding used was Absorb-dri® hardwood chips (Northeastern Products, Inc., Warrenburg, N.Y.). The feed was presterilized Wayne® Sterilizable Lab Meal, provided ad libitum in suspended stainless steel hoppers and replenished at least three times per week. Water, acidified to pH 2.5, was supplied ad libitum from glass bottles. Sipper tubes (Lab Products, Inc.) were suspended through the tops of the cages.

The contaminated bedding was disposed of through an enclosed vacuum line that led to a holding tank from which the bedding was fed periodically into an incinerator. The cages were sanitized twice per week and the feed hoppers twice per month at 82 to 88°C in a tunnel-type cagewasher (Industrial Washing Machine Corp., Mataway, N. J.), using the detergents, Clout® (Pharmacal Research Laboratories, Greenwich, Conn.) or Oxford D'Chlor (Oxford Chemicals, Atlanta, Ga.). The glass bottles and sipper

tubes were sanitized at 82 to 88°C in a tunnel-type bottle washer (Consolidated Equipment Supply Co., Mercersburg, Pa.) three times per week, using a Calgen Commercial Division detergent (St. Louis, Mo.). The racks for the cages were sanitized at or above 82°C in a rack washer (Consolidated Equipment Supply Co.) once per month, using the Calgen Commercial Division detergent, and the filter paper was changed at the same time.

The animal rooms were maintained at 22 to 24°C and 45 to 55% relative humidity. Incoming air was passed through a filter of 65% efficiency and a bag filter of 95% efficiency at the intake, and was expelled without recirculation through a "Z"-type roughing filter of 30% efficiency and a bag system of 90 to 95% efficiency at the exhaust (American Air Filters, Louisville, Ky.; Mine Safety Appliances, Pittsburgh, Pa.). Room air was changed 15 times per hour. The air pressure was maintained negative to a clean hallway and positive to a return hallway. Fluorescent lighting was provided automatically on a 12-hour-per-day cycle.

Rats administered sodium diethyldithiocarbamate and their controls were housed in the same room as rats on feeding studies of the following chemicals:

(CAS 298-00-0) methyl parathion
(CAS 28-66-5) C. I. vat yellow 4

Mice administered sodium diethyldithiocarbamate and their controls were housed in the same room as mice on feeding studies of the following chemicals:

(CAS 128-37-0) butylated hydroxytoluene (BHT)
(CAS 3165-93-3) 4-chloro-o-toluidine hydrochloride
(CAS 19010-66-3) tetraethylthiuram disulfide
(CAS 95-53-4) o-toluidine hydrochloride

E. Subchronic Studies

Subchronic feeding studies were conducted to estimate the maximum tolerated doses (MTD's) of sodium diethyldithiocarbamate, on the basis of which two concentrations (referred to in this report as "low" and "high" doses) were selected for administration in the chronic studies. Groups of five rats and mice of each sex were fed diets containing sodium diethyldithiocarbamate at one of several doses, and groups of five control animals of each species and sex were administered basal diet only. The period of administration of the test chemical was 7 weeks, followed by 1 week of additional observation for rats and male mice; for female mice the period of administration of the test chemical was 12 weeks. Each animal was weighed twice per week. Table 1 shows the survival of animals in each dosed group at the end of the

Table 1. Sodium Diethyldithiocarbamate Subchronic Feeding Studies in Rats and Mice

Male			Female		
Dose (ppm)	Survival(a)	Mean Weight at Week 7 as % of Control	Dose (ppm)	Survival(a)	Mean Weight at Week 7 as % of Control
RATS			RATS		
1,250	5/5	88	1,250	5/5	96
2,500	5/5	95	2,500	5/5	90
5,000	5/5	90	5,000	5/5	90
10,000	5/5	82	10,000	5/5	84
20,000	5/5	67	20,000	5/5	69
40,000	1/5	29	40,000	2/5	39
MICE			MICE		Mean Weight at Week 12 as % of Control
2,500	5/5	105	250	5/5	93
5,000	5/5	97	500	5/5	93
6,000	5/5	78	1,000	5/5	93
8,000	5/5	102	2,500	2/5	91
10,000	5/5	86	5,000	5/5	92
			10,000	5/5	88

(a) Number surviving/number in group.

course of administration and the mean body weights of each dosed group at week 7 or 12, expressed as percentages of mean body weights of controls.

At the end of the subchronic studies, all animals were killed using CO_2 and necropsied. The lowest dose at which histopathologic findings were observed was 1,000 ppm in male and female rats. At this dose a very slight increase in splenic hematopoiesis and a very small amount of vacuolation of renal tubular epithelium were noted. No lesions related to the test chemical were observed in male and female mice dosed at 10,000 ppm.

Ten percent depression in body weight was the major criterion for estimation of MTD's. The doses required to produce this response were determined by the following procedure: first, least squares regressions of mean body weights versus days on study were used to estimate mean body weights of each of the dosed groups at day 49. Next, probits of the percent weights of dosed groups at day 49 relative to weights of corresponding control groups were plotted against the logarithms of the doses, and least squares regressions fitted to the data were used to estimate the doses required to induce 10% depression in weight.

The low and high doses selected for chronic studies were 1,250 and 2,500 ppm for rats; and 500 and 4,000 ppm for mice.

F. Chronic Studies

The test groups, doses administered, and durations of the chronic feeding studies are shown in tables 2 and 3.

G. Clinical and Pathologic Examinations

All animals were observed twice daily. Observations for sick, tumor-bearing, and moribund animals were recorded daily. Clinical examination and palpation for masses were performed each month, and the animals were weighed at least once per month. Moribund animals and animals that survived to the end of the bioassay were killed using CO_2 and necropsied.

The pathologic evaluation consisted of gross and microscopic examination of major tissues, major organs, and all gross lesions. The tissues were preserved in neutral 10% buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following tissues were examined

Table 2. Sodium Diethyldithiocarbamate Chronic Feeding Studies in Rats

Sex and Test Group	Initial No. of Animals(a)	Sodium Diethyl-dithiocarbamate in Diet(b) (ppm)	Time on Study (weeks)
Male			
Matched-Control	16	0	104
Low-Dose	50	1,250	104
High-Dose	50	2,500	104
Female			
Matched-Control	20	0	104
Low-Dose	50	1,250	104
High-Dose	50	2,500	104

(a) All animals were 6 weeks of age when placed on study.

(b) Test and control diets were provided ad libitum 7 days per week.

Table 3. Sodium Diethyldithiocarbamate Chronic Feeding Studies in Mice

Sex and Test Group-	Initial No. of Animals(a)	Sodium Diethyl-dithiocarbamate in Diet(b) (ppm)	Time on Study (weeks)
Male			
Matched-Control	20	0	109
Low-Dose	50	500	108-109
High-Dose	50	4,000	108
Female			
Matched-Control	20	0	109
Low-Dose	50	500	109
High-Dose	50	4,000	108

(a) All animals were 6 weeks of age when placed on study.

(b) Test and control diets were provided *ad libitum* 7 days per week.

microscopically: skin, lungs and bronchi, trachea, bone marrow (femur), spleen, lymph nodes (mesenteric and submandibular), thymus, heart, salivary glands (parotid, sublingual, and submaxillary), liver, pancreas, esophagus, stomach (glandular and nonglandular), small and large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, testis, prostate, mammary gland, uterus, ovary, brain (cerebrum and cerebellum), and all tissue masses. Peripheral blood smears also were made for all animals, whenever possible.

Necropsies were also performed on all animals found dead, unless precluded in whole or in part by autolysis or cannibalization. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and does not necessarily represent the number of animals that were placed on study in each group.

H. Data Recording and Statistical Analyses

Pertinent data on this experiment have been recorded in an automatic data processing system, the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental

design, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969). Data tables were generated for verification of data transcription and for statistical review.

These data were analyzed using the appropriate statistical techniques described in this section. Those analyses of the experimental results that bear on the possibility of carcinogenicity are discussed in the statistical narrative sections.

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) extensions of Cox methods for testing for a dose-related trend. One-tailed P values have been reported for all tests except the departure from linearity test, which is only reported when its two-tailed P value is less than 0.05.

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals in which that site is examined (denominator). In most instances, the denominators included only those animals for which that site was examined histologically. However, when macroscopic examination was required to detect lesions prior to histologic sampling (e.g., skin or mammary tumors), or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970) was used to compare the tumor incidence of a control group with that of a group of dosed animals at each dose level. When results for a number of dosed groups (k) are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality (Miller, 1966) requires that the P value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the

narrative section. It is not, however, presented in the tables, where the Fisher exact P values are shown.

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971), was also used. Under the assumption of a linear trend, this test determines if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend is a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

A time-adjusted analysis was applied when numerous early deaths resulted from causes that were not associated with the formation of tumors. In this analysis, deaths that occurred before the first tumor was observed were excluded by basing the statistical tests on animals that survived at least 52 weeks, unless a tumor was found at the anatomic site of interest before week 52. When such an early tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which the first tumor was found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

When appropriate, life-table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week during which an animal died naturally or was sacrificed was entered as the time point of tumor observation. Cox's methods of comparing these curves were used for two groups; Tarone's extension to testing for linear trend was used for three groups. The statistical tests for the incidence of tumors which used life-table methods were one-tailed and, unless otherwise noted, in the direction of a positive dose relationship. Significant departures from linearity (P less than 0.05, two-tailed test) were also noted.

The approximate 95 percent confidence interval for the relative risk of each dosed group compared with its control was calculated from the exact interval on the odds ratio (Gart, 1971). The relative risk is defined as p_t/p_c where p_t is the true binomial probability of the incidence of a specific type of tumor in a dosed group of animals and p_c is the true probability of the spontaneous incidence of the same type of tumor in a control group. The hypothesis of equality between the true proportion of a specific tumor in a dosed group and the proportion in a control group corresponds to a relative risk of unity. Values in excess

of unity represent the condition of a larger proportion in the dosed group than in the control.

The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that in approximately 95% of a large number of identical experiments, the true ratio of the risk in a dosed group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically significant result (P less than 0.025 one-tailed test when the control incidence is not zero, P less than 0.050 when the control incidence is zero) has occurred. When the lower limit is less than unity, but the upper limit is a greater than unity, the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of the induction of tumors by the test chemical, which could not be detected under the conditions of this test.

III. RESULTS - RATS

A. Body Weights and Clinical Signs (Rats)

Mean body weights of the high-dose males were lower than those of the corresponding controls; mean body weights of the low-dose males were essentially unaffected by administration of the test chemical (figure 1). Mean body weights of both the high- and low-dose female rats were lower than those of the corresponding controls, and were dose related throughout the bioassay. Other clinical signs occurred at low incidences in control and dosed rats.

B. Survival (Rats)

The Kaplan and Meier curves for estimating the probabilities of survival for male and female rats administered sodium diethyldithiocarbamate in the diet at the doses of this bioassay, together with those of the matched controls, are shown in figure 2. The result of the Tarone test for dose-related trend in mortality is not significant in either sex.

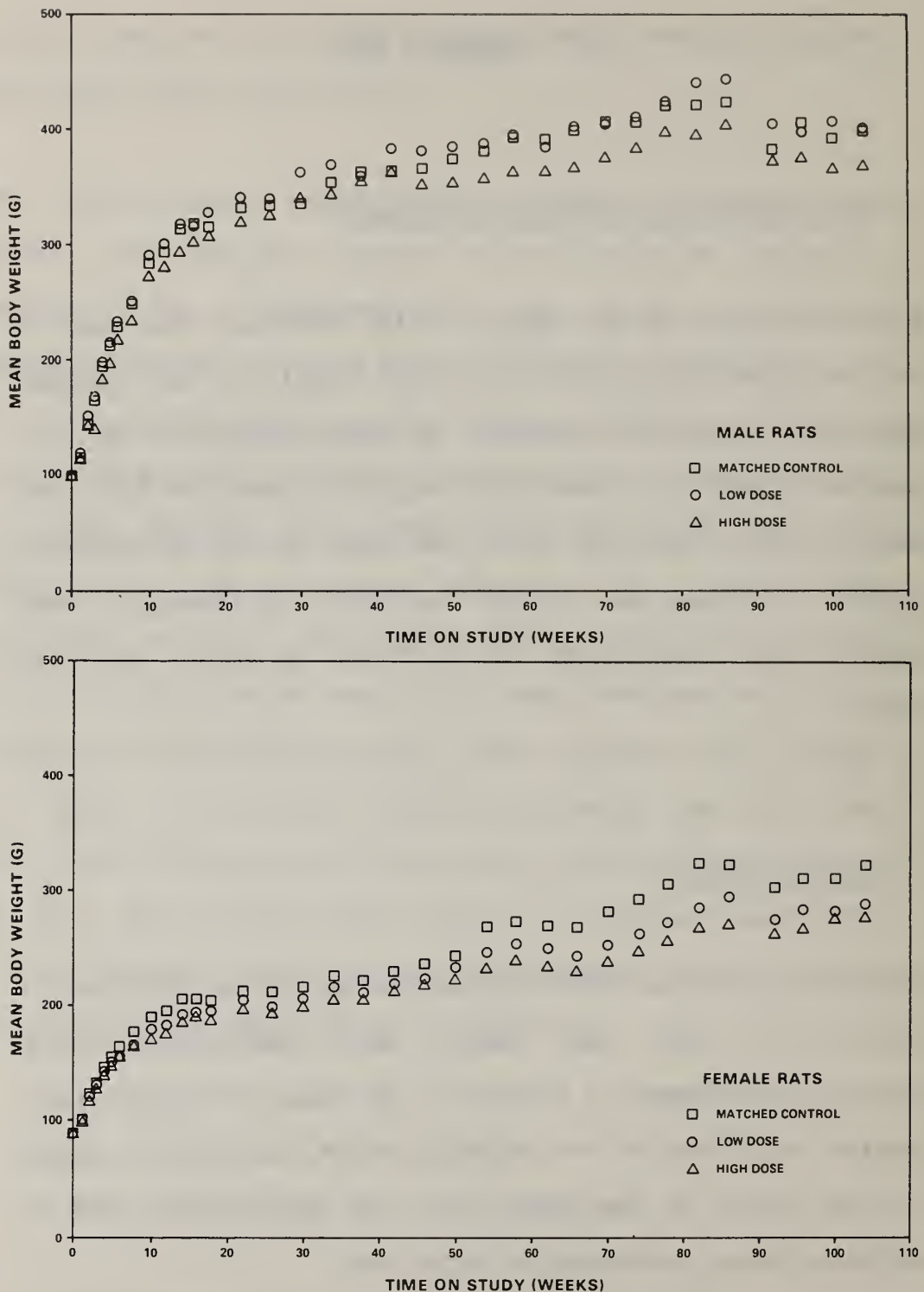


Figure 1. Growth Curves for Rats Administered Sodium Diethyldithiocarbamate in the Diet

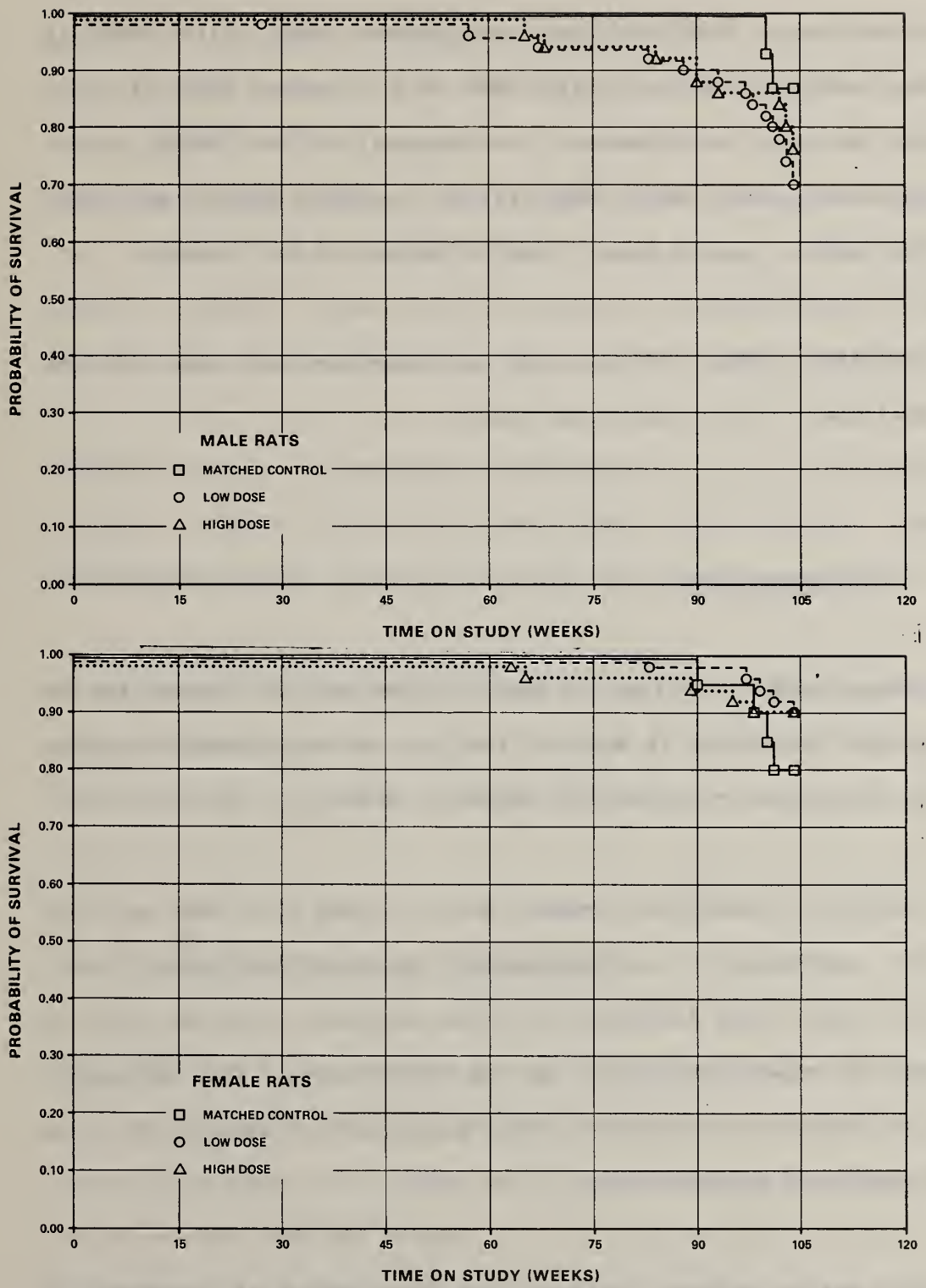


Figure 2. Survival Curves for Rats Administered Sodium Diethyldithiocarbamate in the Diet

In male rats, 38/50 (76%) of the high-dose group, 35/50 (70%) of the low-dose group, and 14/16 (88%) of the control group lived to the end of the bioassay. In females, 45/50 (90%) of the high-dose group, 45/50 (90%) of the low-dose group, and 16/20 (80%) of the control group lived to the end of the bioassay.

Sufficient numbers of rats of each sex were at risk for the development of late-appearing tumors.

C. Pathology (Rats)

Histopathologic findings on neoplasms in rats are summarized in Appendix A, tables A1 and A2; findings on nonneoplastic lesions are summarized in Appendix C, tables C1 and C2.

A variety of neoplasms commonly seen in aged F344 rats occurred with approximately equal frequency in dosed and control rats. There were a few instances in which neoplasms occurred only, or with increased frequency, in the dosed rats. The incidence, distribution, and nature of these neoplasms are similar to those occurring in aged F344 rats.

There was an unusual incidence and distribution of cataracts of

the eye in the dosed female rats. Cataracts were observed in the eyes of 0/20 control, 14/50 low-dose, and 6/50 high-dose female rats. Only eyes that were grossly abnormal were required to be examined microscopically. Eyes without gross abnormalities were not processed for histopathologic examination. Since only grossly abnormal eyes were examined microscopically, the significance of this observation is not known.

Several other inflammatory, degenerative, and proliferative lesions commonly seen in aged F344 rats occurred with approximately equal frequency in dosed and control animals.

Based on the histopathologic examination, the sodium diethyldithiocarbamate administered in the diet at the doses used was not carcinogenic for male or female F344 rats.

D. Statistical Analyses of Results (Rats)

Tables E1 and E2 in Appendix E contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals of one group and at an incidence of at least 5% in one or more than one group.

The result of the Cochran-Armitage test for positive dose-related trend in incidences of tumors and the results of the Fisher exact test comparing the incidence of tumors in the control group with that in each dosed group in the positive direction are not significant in either sex.

Significant results in the negative direction are observed in the incidences of C-cell tumors of the thyroid and islet-cell tumors of the pancreas in male rats, as well as in the incidences of pituitary tumors and mammary gland tumors in female rats, in which the incidences in the control group exceed those in the dosed groups.

In each of the 95% confidence intervals for relative risk, shown in the tables, the value of one or less than one is included; this indicates the absence of significant positive results. It should also be noted that each of the intervals, except those for the incidences of fibroadenoma of the mammary gland in the high-dose female rats and adenomas of the pituitary in the low-dose females, has an upper limit greater than one, indicating the theoretical possibility of the induction of tumors by sodium diethyldithiocarbamate, which could not be detected under the conditions of this test.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

Mean body weights of the dosed male and female mice were lower than those of corresponding control groups, and were dose related throughout the bioassay (figure 3).

B. Survival (Mice)

The Kaplan and Meier curves for estimating the probabilities of survival for male and female mice administered sodium diethyldithiocarbamate in the diet at the doses of this bioassay, together with those of the matched controls, are shown in figure 4. The result of the Tarone test for dose-related trend in mortality is not significant in either sex. In female mice, the result of the Cox test comparing the high-dose and matched-control groups is significant ($P = 0.025$), but in the negative direction.

In male mice, 38/50 (76%) of the high-dose group, 41/50 (82%) of the low-dose group, and 17/20 (85%) of the control group lived to

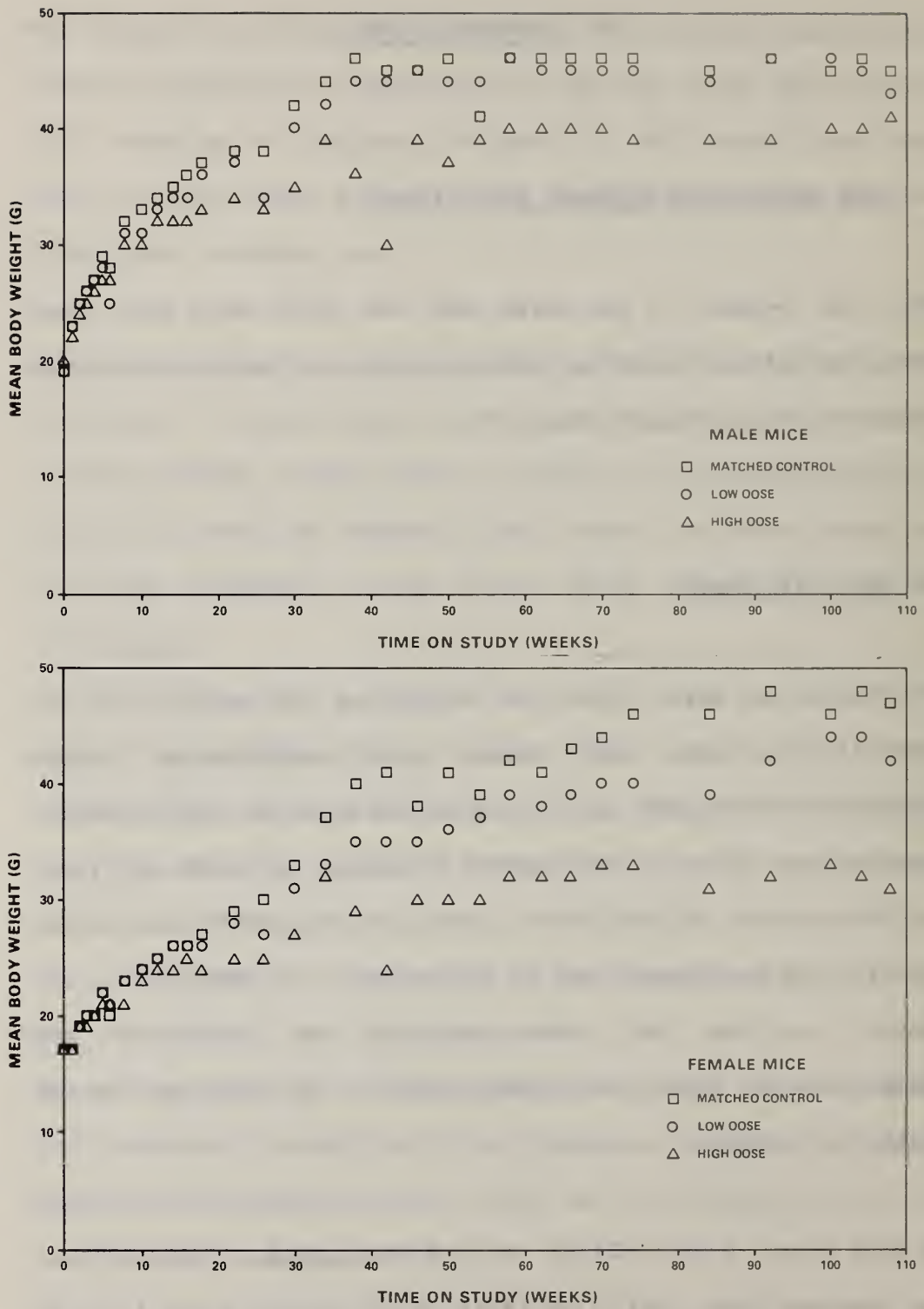


Figure 3. Growth Curves for Mice Administered Sodium Diethyldithiocarbamate in the Diet

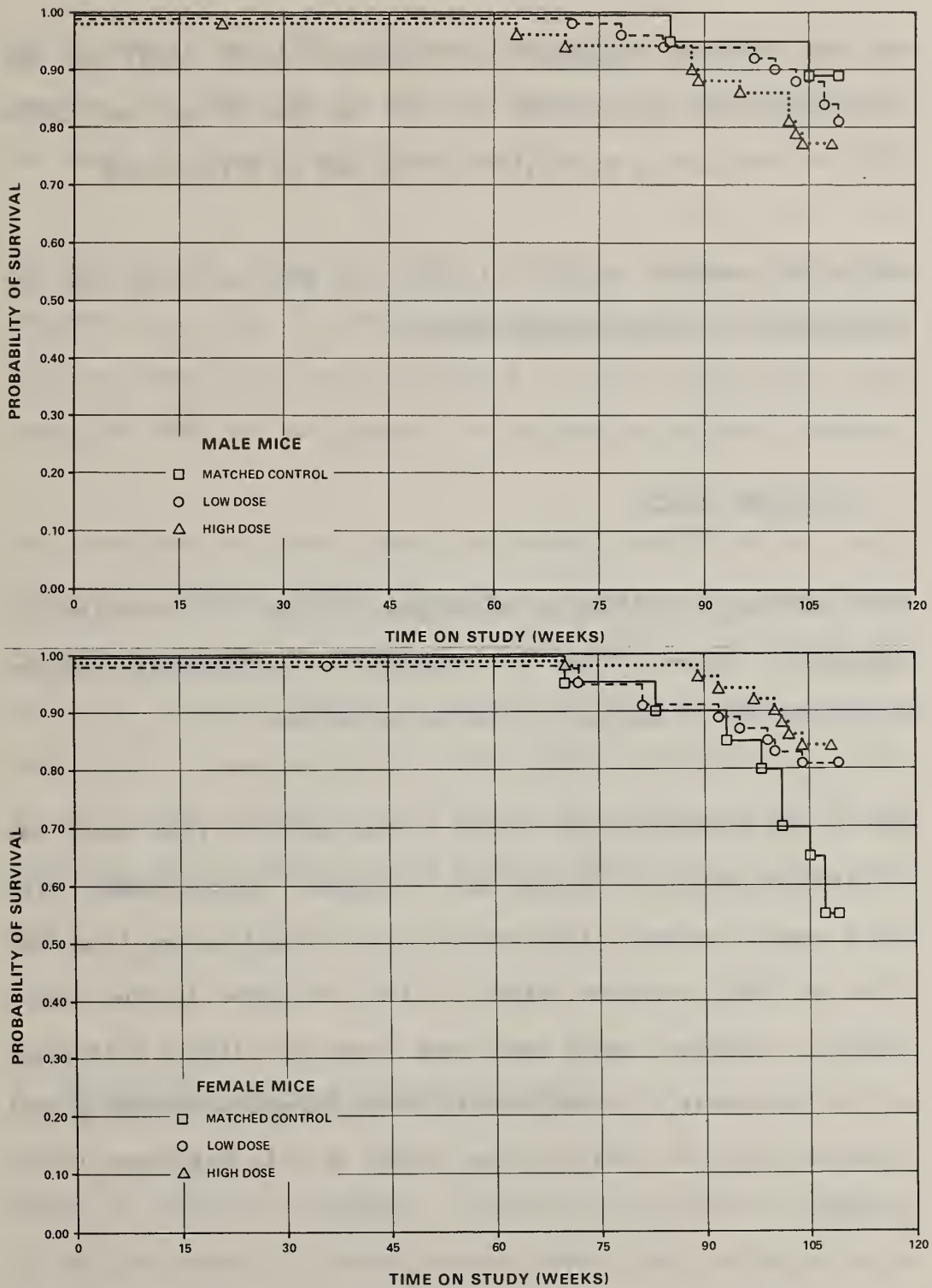


Figure 4. Survival Curves for Mice Administered Sodium Diethyldithiocarbamate in the Diet

the end of the bioassay. In females, 42/50 (84%) of the high-dose group, 40/50 (80%) of the low-dose group, and 11/20 (55%) of the control group lived to the end of the bioassay.

Sufficient numbers of mice of each sex were at risk for the development of late-appearing tumors.

C. Pathology (Mice)

Histopathologic findings on neoplasms in mice are summarized in Appendix B, tables B1 and B2; findings on nonneoplastic lesions are summarized in Appendix D, tables D1 and D2.

One of the most prevalent tumors in the mice in this study was alveolar/bronchiolar adenoma or carcinoma. Among female mice there were 15 animals with these tumors in dosed groups (low-dose 7/49, or 14%; high-dose 8/50, or 16%) and none in the female controls. However, among male mice there was little difference in the incidences of these tumors in the dosed and control groups (controls 6/19, or 32%; low-dose 14/50, or 28%; high-dose 14/49, or 28%).

There were also a number of hepatocellular tumors in both dosed

and control mice. The incidence was higher in males than in females, and there was no apparent increase in the incidence of the tumors in dosed animals over controls.

In addition to these neoplastic lesions, other tumors were observed that were of single occurrence or very low incidence. All were tumors that may be expected in mice of this strain and, therefore, were not considered to be related to the test compound.

The occurrence of lung tumors in female dosed mice and their absence in control females was not believed to be significant, because of the smaller number of control animals and because the incidence of these tumors was higher in control males than in dosed males. Based on the histopathologic examination, there was no conclusive evidence in this study that sodium diethyldithiocarbamate was carcinogenic when given to B6C3F1 mice at the doses used.

D. Statistical Analyses of Results (Mice)

Tables F1 and F2 in Appendix F contain the statistical analyses of the incidences of those primary tumors that occurred in at

least two animals of one group and at an incidence of at least 5% in one or more than one group.

The results of the Cochran-Armitage test for positive dose-related trend in the incidence of tumors and the results of the Fisher exact test comparing the incidence of tumors in the control group with that in each dosed group in the positive direction are not significant in either sex.

In female mice, the results of the Fisher exact test show that the incidence of lymphomas in the low-dose group is significantly lower ($P = 0.009$) than that in the control group. A significant trend ($P = 0.037$) in the negative direction is also observed in the incidence of pituitary tumors in the females.

In each of the 95% confidence intervals for relative risk, shown in the tables, the value of one or less than one is included; this indicates the absence of significant positive results. It should also be noted that each of the intervals, except that for the incidence of lymphoma in low-dose female mice, has an upper limit greater than one, indicating the theoretical possibility of the induction of tumors by sodium diethyldithiocarbamate, which could not be detected under the conditions of this test.

V. DISCUSSION

Mean body weights of all dosed groups of rats and mice were lower than those of corresponding controls and were dose related throughout the bioassay, except those of the low-dose male rats, which were essentially unaffected by administration of the test chemical. However, survivals of the dosed rats and mice were unaffected, and no other clinical signs could be related to administration of the test chemical; thus, the animals may have been able to tolerate higher doses. The survivals in the dosed and control groups of rats and mice were 74% or greater, except in the control female mice (55%). Sufficient numbers of animals were at risk for the development of late-appearing tumors.

No tumors occurred in the rats or mice of either sex at incidences that were significantly higher in the dosed groups than in the control groups. The incidences of C-cell tumors of the thyroid and islet-cell tumors of the pancreas in the male rats, pituitary tumors and mammary gland tumors in the female rats, lymphomas in the female mice, and pituitary tumors in the female mice were lower in the dosed groups than in the corresponding control groups (based on dose-related trends, direct comparisons of dosed and control groups, or both).

A compound-related effect is suggested by the incidence of cataracts in the female rats; however, the interpretation of this lesion is limited because all eyes were not prepared for histopathologic examination.

In other tests for tumorigenicity, Innes et al. (1969) reported that when sodium diethyldithiocarbamate was administered at 215 mg/kg by stomach tube for 3 weeks, then in the diet at 692 ppm for 18 months, to each of two different hybrids of mice (C57BL/6 x C3H/Anf and C57BL/6 x AKR), elevated incidences of hepatomas in males of the first hybrids (P less than 0.05) and of pulmonary adenomas in males of the second hybrids (P less than 0.01) were observed (International Agency for Research on Cancer, 1976; National Technical Information Service, 1968).

It is concluded that under the conditions of this bioassay, sodium diethyldithiocarbamate was not carcinogenic for F344 rats or B6C3F1 mice of either sex.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS ADMINISTERED SODIUM DIETHYLDITHIOCARBAMATE IN THE DIET

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED SODIUM DIETHYLDITHIOCARBAMATE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	16	50	50
ANIMALS NECROPSIED	16	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	16	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(16)	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (6%)		
*SUBCUT TISSUE	(16)	(50)	(50)
FIBROMA	1 (6%)		
LIPOMA		1 (2%)	
NEUROFIBROSARCOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(16)	(50)	(50)
SQUAMOUS CELL CARCINOMA			1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (13%)	2 (4%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		2 (4%)	3 (6%)
C-CELL CARCINOMA, METASTATIC			1 (2%)
SARCOMA, NOS, METASTATIC		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(16)	(50)	(50)
LEUKEMIA,NOS		4 (8%)	2 (4%)
UNDIFFERENTIATED LEUKEMIA	3 (19%)	9 (18%)	12 (24%)
*BLOOD	(16)	(50)	(50)
LEUKEMIA,NOS	1 (6%)		
#MEDIASTINAL L.NODE	(15)	(50)	(50)
SARCOMA, NOS, METASTATIC			1 (2%)
MESOTHELIOMA, METASTATIC			1 (2%)
CIRCULATORY SYSTEM			
#HEART	(16)	(50)	(50)
SARCOMA, NOS		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(16)	(50)	(50)
NEOPLASTIC NODULE		1 (2%)	
#SMALL INTESTINE	(16)	(49)	(48)
ADENOCARCINOMA, NOS			1 (2%)
#LARGE INTESTINE	(16)	(50)	(49)
LIPOMA			1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(16)	(50)	(48)
ADENOMA, NOS	5 (31%)	7 (14%)	6 (13%)
#ADRENAL	(16)	(50)	(50)
CORTICAL ADENOMA		2 (4%)	
CORTICAL CARCINOMA		1 (2%)	
PHEOCHROMOCYTOMA	2 (13%)	2 (4%)	5 (10%)
#THYROID	(15)	(50)	(49)
FOLLICULAR-CELL ADENOMA		4 (8%)	2 (4%)
FOLLICULAR-CELL CARCINOMA		2 (4%)	1 (2%)
C-CELL ADENOMA	3 (20%)	9 (18%)	2 (4%)
C-CELL CARCINOMA		1 (2%)	1 (2%)
#PARATHYROID	(14)	(45)	(43)
ADENOMA, NOS		1 (2%)	
#PANCREATIC ISLETS	(16)	(49)	(48)
ISLET-CELL ADENOMA	3 (19%)	2 (4%)	1 (2%)
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(16)	(50)	(50)
CARCINOMA, NOS		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#TESTIS	(16)	(50)	(50)
INTERSTITIAL-CELL TUMOR	14 (88%)	42 (84%)	44 (88%)
INTERSTITIAL-CELL TUMOR, MALIGNA			1 (2%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(16)	(50)	(50)
MENINGIOMA			1 (2%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(16)	(50)	(50)
INTERSTITIAL-CELL TUMOR, METASTA			1 (2%)
SARCOMA, NOS			1 (2%)
*MESENTERY	(16)	(50)	(50)
LIPOMA	1 (6%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(16)	(50)	(50)
MESOTHELIOMA, NOS		2 (4%)	1 (2%)
MESOTHELIOMA, MALIGNANT			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	16	50	50
NATURAL DEATH@	1	11	6
MORIBUND SACRIFICE	1	4	6
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	14	35	38
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	16	48	49
TOTAL PRIMARY TUMORS	36	96	90
TOTAL ANIMALS WITH BENIGN TUMORS	15	45	44
TOTAL BENIGN TUMORS	31	72	64
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	20	22
TOTAL MALIGNANT TUMORS	5	21	25
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	4
TOTAL SECONDARY TUMORS		1	5
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT		3	1
TOTAL UNCERTAIN TUMORS		3	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS ADMINISTERED SODIUM DIETHYLDITHIOCARBAMATE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (5%)		
SQUAMOUS CELL CARCINOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	2 (10%)	3 (6%)	4 (8%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(50)	(50)
LEUKEMIA,NOS		1 (2%)	1 (2%)
UNDIFFERENTIATED LEUKEMIA	1 (5%)	4 (8%)	1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(50)	(50)
NEOPLASTIC NODULE	1 (5%)		
#ESOPHAGUS	(20)	(49)	(49)
SQUAMOUS CELL CARCINOMA			1 (2%)
URINARY SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(50)	(50)
ADENOMA, NOS	9 (45%)	9 (18%)	16 (32%)
#ADRENAL	(20)	(49)	(49)
CORTICAL ADENOMA		2 (4%)	2 (4%)
PHEOCHROMOCYTOMA			1 (2%)
GANGLIONEUROMA	1 (5%)		
#THYROID	(20)	(49)	(50)
FOLLICULAR-CELL ADENOMA		1 (2%)	1 (2%)
C-CELL ADENOMA	2 (10%)	1 (2%)	5 (10%)
C-CELL CARCINOMA		1 (2%)	
#PANCREATIC ISLETS	(20)	(49)	(50)
ISLET-CELL ADENOMA	1 (5%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
FIBROADENOMA	3 (15%)	3 (6%)	
*CLITORAL GLAND	(20)	(50)	(50)
ADENOMA, NOS			1 (2%)
#UTERUS	(20)	(50)	(49)
LEIOMYOSARCOMA	1 (5%)		
ENDOMETRIAL STROMAL POLYP	3 (15%)	7 (14%)	10 (20%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(50)	(50)
SARCOMA, NOS		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	1	4	3
MORIBUND SACRIFICE	3	1	2
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	16	45	45
ANIMAL MISSING			
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	17	26	34
TOTAL PRIMARY TUMORS	25	33	44
TOTAL ANIMALS WITH BENIGN TUMORS	15	20	31
TOTAL BENIGN TUMORS	22	26	40
TOTAL ANIMALS WITH MALIGNANT TUMORS	2	7	4
TOTAL MALIGNANT TUMORS	2	7	4
TOTAL ANIMALS WITH SECONDARY TUMORS#			
TOTAL SECONDARY TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT	1		
TOTAL UNCERTAIN TUMORS	1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE ADMINISTERED SODIUM DIETHYLDITHIOCARBAMATE IN THE DIET

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED SODIUM DIETHYLDITHIOCARBAMATE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	1		1
ANIMALS NECROPSIED	19	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	19	50	49
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(19)	(50)	(49)
HEPATOCELLULAR CARCINOMA, METAST		3 (6%)	
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (5%)	4 (8%)	6 (12%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	5 (26%)	10 (20%)	8 (16%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(19)	(50)	(49)
MALIGNANT LYMPHOMA, NOS	2 (11%)	4 (8%)	4 (8%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE		2 (4%)	
LYMPHOCYTIC LEUKEMIA			1 (2%)
#SPLEEN	(19)	(50)	(49)
HEMANGIOSARCOMA	1 (5%)	2 (4%)	1 (2%)
MALIGNANT LYMPHOMA, NOS			1 (2%)
#MESENTERIC L. NODE	(19)	(50)	(48)
MALIGNANT LYMPHOMA, NOS		1 (2%)	2 (4%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
#LUNG	(19)	(50)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
#SMALL INTESTINE	(19)	(50)	(49)
MALIGNANT LYMPHOMA, NOS		5 (10%)	
CIRCULATORY SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(19)	(50)	(49)
HEPATOCELLULAR ADENOMA	2 (11%)	2 (4%)	3 (6%)
HEPATOCELLULAR CARCINOMA	5 (26%)	9 (18%)	8 (16%)
HEMANGIOSARCOMA		1 (2%)	
#SMALL INTESTINE	(19)	(50)	(49)
ADENOCARCINOMA, NOS		1 (2%)	1 (2%)
URINARY SYSTEM			
#URINARY BLADDER	(19)	(50)	(48)
TRANSITIONAL-CELL CARCINOMA		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(19)	(49)	(45)
ADENOMA, NOS	1 (5%)		
#ADRENAL	(19)	(49)	(49)
PHEOCHROMOCYTOMA	1 (5%)		
#THYROID	(19)	(49)	(48)
FOLLICULAR-CELL ADENOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
NONE			
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(19)	(50)	(49)
ADENOMA, NOS	1 (5%)		1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*MESENTERY	(19)	(50)	(49)
LIPOMA	2 (11%)	2 (4%)	1 (2%)
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	2	9	11
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	17	41	38
ANIMAL MISSING	1		1
@ INCLUDES AUTOLYZED ANIMALS			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	13	37	30
TOTAL PRIMARY TUMORS	21	45	39
TOTAL ANIMALS WITH BENIGN TUMORS	7	7	11
TOTAL BENIGN TUMORS	8	9	11
TOTAL ANIMALS WITH MALIGNANT TUMORS	9	32	23
TOTAL MALIGNANT TUMORS	13	36	28
TOTAL ANIMALS WITH SECONDARY TUMORS#		3	
TOTAL SECONDARY TUMORS		3	
TOTAL ANIMALS WITH TUMORS UNCERTAIN- BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN- PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE ADMINISTERED SODIUM DIETHYLDITHIOCARBAMATE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	20	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(20)	(49)	(50)
PAPILLOMA, NOS		1 (2%)	
FIBROSARCOMA			1 (2%)
NEUROFIBROSARCOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(20)	(49)	(50)
CARCINOMA, NOS, METASTATIC		1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA		4 (8%)	4 (8%)
ALVEOLAR/BRONCHIOLAR CARCINOMA		3 (6%)	4 (8%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(20)	(49)	(50)
MALIGNANT LYMPHOMA, NOS	7 (35%)	4 (8%)	10 (20%)
#SPLEEN	(20)	(48)	(50)
HEMANGIOSARCOMA		1 (2%)	
MALIGNANT LYMPHOMA, NOS			1 (2%)
#MESENTERIC L. NODE	(19)	(46)	(49)
MALIGNANT LYMPHOMA, NOS	1 (5%)	1 (2%)	
#SMALL INTESTINE	(20)	(49)	(50)
MALIGNANT LYMPHOMA, NOS	1 (5%)	1 (2%)	2 (4%)
#THYMUS	(15)	(39)	(44)
MALIGNANT LYMPHOMA, NOS		1 (3%)	
CIRCULATORY SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER	(20)	(49)	(50)
HEPATOCELLULAR ADENOMA		2 (4%)	2 (4%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY	(19)	(47)	(49)
CARCINOMA,NOS	1 (5%)	1 (2%)	
ADENOMA, NOS	1 (5%)	1 (2%)	
#ADRENAL	(20)	(49)	(50)
CORTICAL ADENOMA		2 (4%)	
CORTICAL CARCINOMA			1 (2%)
#THYROID	(20)	(49)	(48)
FOLLICULAR-CELL ADENOMA			1 (2%)
FOLLICULAR-CELL CARCINOMA	1 (5%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(49)	(50)
ADENOCARCINOMA, NOS	1 (5%)		
#UTERUS	(20)	(49)	(49)
LEIOMYOMA			1 (2%)
ENDOMETRIAL STROMAL POLYP			1 (2%)
HEMANGIOSARCOMA		1 (2%)	
#OVARY	(20)	(49)	(48)
CARCINOMA,NOS		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(20)	(49)	(50)
FIBROSARCOMA	1 (5%)		
*MESENTERY	(20)	(49)	(50)
LIPOMA			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(49)	(50)
FIBROSARCOMA	1 (5%)		
THORACIC CAVITY			
NEUROFIBROSARCOMA			1
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	20	50	50
NATURAL DEATH@	9	8	7
MORIBUND SACRIFICE		1	1
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	11	40	42
ANIMAL MISSING		1	

@ INCLUDES AUTOLYZED ANIMALS

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	13	20	26
TOTAL PRIMARY TUMORS	15	24	31
TOTAL ANIMALS WITH BENIGN TUMORS	1	8	9
TOTAL BENIGN TUMORS	1	10	10
TOTAL ANIMALS WITH MALIGNANT TUMORS	12	13	20
TOTAL MALIGNANT TUMORS	14	14	21
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	
TOTAL SECONDARY TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS ADMINISTERED SODIUM DIETHYLDITHIOCARBAMATE IN THE DIET

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED SODIUM DIETHYLDITHIOCARBAMATE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	16	50	50
ANIMALS NECROPSIED	16	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	16	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(16)	(50)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)	1 (2%)
INFLAMMATION, ACUTE			1 (2%)
HYPERKERATOSIS		1 (2%)	1 (2%)
ACANTHOSIS		1 (2%)	1 (2%)
*SUBCUT TISSUE	(16)	(50)	(50)
HEMATOMA, NOS			1 (2%)
INFLAMMATION, NOS	1 (6%)		
ABSCESS, NOS	1 (6%)	1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
#TRACHEA	(16)	(50)	(50)
INFLAMMATION, ACUTE		1 (2%)	
#LUNG	(16)	(50)	(50)
HEMORRHAGE		1 (2%)	
BRONCHOPNEUMONIA, ACUTE		1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)
GRANULOMA, NOS			3 (6%)
ALVEOLAR MACROPHAGES			2 (4%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(16)	(50)	(50)
INFARCT, NOS		1 (2%)	
LIPOIDOSIS	1 (6%)		
HEMOSIDEROSIS		1 (2%)	
LYMPHOID DEPLETION	1 (6%)	2 (4%)	1 (2%)
HYPERPLASIA, LYMPHOID		1 (2%)	1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
HEMATOPOIESIS		1 (2%)	
#MANDIBULAR L. NODE	(15)	(50)	(50)
LYMPHANGIECTASIS		3 (6%)	
EDEMA, NOS		1 (2%)	
LYMPHOID DEPLETION		2 (4%)	
CIRCULATORY SYSTEM			
#HEART	(16)	(50)	(50)
PERIARTERITIS		1 (2%)	
PERIVASCULITIS			1 (2%)
#HEART/ATRIUM	(16)	(50)	(50)
THROMBOSIS, NOS		5 (10%)	2 (4%)
#MYOCARDIUM	(16)	(50)	(50)
INFLAMMATION, CHRONIC		2 (4%)	2 (4%)
FIBROSIS	3 (19%)	11 (22%)	
*PULMONARY ARTERY	(16)	(50)	(50)
MINERALIZATION		10 (20%)	4 (8%)
*PANCREATIC ARTERY,	(16)	(50)	(50)
HYPERTROPHY, NOS	1 (6%)		
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(16)	(50)	(49)
INFLAMMATION, CHRONIC		2 (4%)	
#LIVER	(16)	(50)	(50)
HEMORRHAGE		1 (2%)	
NECROSIS, NOS		4 (8%)	3 (6%)
CYTOPLASMIC VACUOLIZATION	2 (13%)	3 (6%)	2 (4%)
BASOPHILIC CYTO CHANGE	1 (6%)	5 (10%)	2 (4%)
EOSINOPHILIC CYTO CHANGE	1 (6%)		
CLEAR-CELL CHANGE	1 (6%)		1 (2%)
NODULAR REGENERATION			1 (2%)
#LIVER/CENTRILOBULAR	(16)	(50)	(50)
DEGENERATION, NOS		3 (6%)	2 (4%)
#BILE DUCT	(16)	(50)	(50)
INFLAMMATION, NOS	1 (6%)	3 (6%)	15 (30%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
HYPERPLASIA, NOS	12 (75%)	44 (88%)	34 (68%)
#PANCREATIC ACINUS	(16)	(49)	(48)
FIBROSIS		1 (2%)	
ATROPHY, NOS	2 (13%)	6 (12%)	5 (10%)
#STOMACH	(16)	(50)	(50)
INFLAMMATION, NOS			1 (2%)
ULCER, NOS			2 (4%)
INFLAMMATION, ACUTE			1 (2%)
#PEYERS PATCH	(16)	(49)	(48)
HYPERPLASIA, LYMPHOID			1 (2%)
URINARY SYSTEM			
#KIDNEY	(16)	(50)	(50)
HAMARTOMA		1 (2%)	
HYDRONEPHROSIS			2 (4%)
PYELONEPHRITIS, NOS			1 (2%)
INFLAMMATION, CHRONIC	16 (100%)	43 (86%)	43 (86%)
PERIARTERITIS		1 (2%)	
INFARCT, HEALED			1 (2%)
PIGMENTATION, NOS		5 (10%)	3 (6%)
#KIDNEY/CORTEX	(16)	(50)	(50)
CYST, NOS	1 (6%)		1 (2%)
#KIDNEY/PELVIS	(16)	(50)	(50)
PERIARTERITIS		1 (2%)	
HYPERPLASIA, EPITHELIAL			1 (2%)
#URINARY BLADDER	(16)	(50)	(50)
CAST, NOS	3 (19%)		
INFLAMMATION, NOS			1 (2%)
INFLAMMATION, CHRONIC	1 (6%)		1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(16)	(50)	(48)
CYST, NOS		2 (4%)	
HEMORRHAGIC CYST			1 (2%)
#ADRENAL	(16)	(50)	(50)
PERIARTERITIS		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#ADRENAL/CAPSULE	(16)	(50)	(50)
THROMBOSIS, NOS		1 (2%)	
#ADRENAL CORTEX	(16)	(50)	(50)
LIPOIDOSIS		2 (4%)	1 (2%)
HYPERPLASIA, NOS		3 (6%)	3 (6%)
#ADRENAL MEDULLA	(16)	(50)	(50)
NECROSIS, NOS			1 (2%)
HYPERPLASIA, NOS			1 (2%)
#THYROID	(15)	(50)	(49)
CYST, NOS		1 (2%)	1 (2%)
CYSTIC FOLLICLES		1 (2%)	1 (2%)
HYPERPLASIA, C-CELL		4 (8%)	14 (29%)
#PANCREATIC ISLETS	(16)	(49)	(48)
HYPERPLASIA, NOS			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(16)	(50)	(50)
DILATATION/DUCTS		1 (2%)	
#PROSTATE	(16)	(49)	(50)
MINERALIZATION			1 (2%)
INFLAMMATION, SUPPURATIVE			1 (2%)
INFLAMMATION, ACUTE	4 (25%)	12 (24%)	7 (14%)
INFLAMMATION, CHRONIC		1 (2%)	
#TESTIS	(16)	(50)	(50)
ATROPHY, NOS	1 (6%)		
HYPERPLASIA, INTERSTITIAL CELL		2 (4%)	
#TESTIS/TUBULE	(16)	(50)	(50)
MINERALIZATION	1 (6%)		
NERVOUS SYSTEM			
#BRAIN	(16)	(50)	(50)
MINERALIZATION		1 (2%)	
HEMORRHAGE	1 (6%)	1 (2%)	2 (4%)
SPECIAL SENSE ORGANS			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(16)	(50)	(50)
PERIARTERITIS	2 (13%)	3 (6%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		1	
AUTO/NECROPSY/HISTO PERF			1

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS ADMINISTERED SODIUM DIETHYLDITHIOCARBAMATE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS NECROPSIED	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	50	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(20)	(50)	(50)
BRONCHOPNEUMONIA, ACUTE			1 (2%)
GRANULOMA, NOS		3 (6%)	
PIGMENTATION, NOS		1 (2%)	
ALVEOLAR MACROPHAGES		7 (14%)	10 (20%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (5%)	3 (6%)	3 (6%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(20)	(50)	(50)
FIBROSIS, FOCAL		1 (2%)	
PIGMENTATION, NOS	2 (10%)		
HYPERPLASIA, LYMPHOID		2 (4%)	
HEMATOPOIESIS		4 (8%)	3 (6%)
#MANDIBULAR L. NODE	(20)	(50)	(50)
LYMPHANGIECTASIS		2 (4%)	1 (2%)
PIGMENTATION, NOS		1 (2%)	
#MESENTERIC L. NODE	(20)	(50)	(50)
HYPERPLASIA, LYMPHOID		1 (2%)	1 (2%)
CIRCULATORY SYSTEM			
#HEART	(20)	(50)	(50)
FIBROSIS			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTRDL	LOW DDSE	HIGH DDSE
PERIARTERITIS		1 (2%)	1 (2%)
#HEART/ATRIUM	(20)	(50)	(50)
THROMBOSIS, NOS		3 (6%)	1 (2%)
#MYOCARDIUM	(20)	(50)	(50)
INFLAMMATION, FOCAL		1 (2%)	1 (2%)
INFLAMMATION, CHRONIC		3 (6%)	1 (2%)
FIBROSIS	3 (15%)	4 (8%)	3 (6%)
*PULMONARY ARTERY	(20)	(50)	(50)
MINERALIZATION	5 (25%)	17 (34%)	3 (6%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(20)	(50)	(50)
INFLAMMATION, CHRONIC		1 (2%)	1 (2%)
#LIVER	(20)	(50)	(50)
INFLAMMATION, NOS		4 (8%)	6 (12%)
INFLAMMATION, FOCAL		1 (2%)	
GRANULOMA, NOS			3 (6%)
NECROSIS, NOS		1 (2%)	
CYTOPLASMIC VACUOLIZATION	4 (20%)	2 (4%)	1 (2%)
BASOPHILIC CYTO CHANGE	16 (80%)	43 (86%)	41 (82%)
EOSINOPHILIC CYTO CHANGE		1 (2%)	
#LIVER/CENTRILOBULAR	(20)	(50)	(50)
DEGENERATION, NOS		2 (4%)	
#BILE DUCT	(20)	(50)	(50)
INFLAMMATION, NOS	4 (20%)	13 (26%)	10 (20%)
HYPERPLASIA, NOS	4 (20%)	15 (30%)	7 (14%)
#PANCREATIC ACINUS	(20)	(49)	(50)
ATROPHY, NOS	5 (25%)	4 (8%)	8 (16%)
#ESOPHAGUS	(20)	(49)	(49)
HYPERKERATOSIS		1 (2%)	
#STOMACH	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)		
ULCER, NOS	1 (5%)		
#PEYERS PATCH	(20)	(50)	(50)
HYPERPLASIA, LYMPHOID	1 (5%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#KIDNEY	(20)	(50)	(50)
MINERALIZATION		1 (2%)	2 (4%)
HYDRONEPHROSIS		1 (2%)	
CYST, NOS		1 (2%)	
INFLAMMATION, CHRONIC	12 (60%)	13 (26%)	5 (10%)
NEPHROSIS, NOS	1 (5%)		
#KIDNEY/PELVIS	(20)	(50)	(50)
MINERALIZATION	1 (5%)	7 (14%)	3 (6%)
#URINARY BLADDER	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)		
HYPERPLASIA, EPITHELIAL	1 (5%)	1 (2%)	1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(20)	(50)	(50)
CYST, NOS	3 (15%)	4 (8%)	2 (4%)
ANGIECTASIS	1 (5%)	3 (6%)	2 (4%)
#ADRENAL	(20)	(49)	(49)
LIPOIDOSIS	1 (5%)		
ANGIECTASIS		1 (2%)	
#ADRENAL CORTEX	(20)	(49)	(49)
LIPOIDOSIS	3 (15%)	2 (4%)	2 (4%)
HYPERPLASIA, NOS	2 (10%)	3 (6%)	3 (6%)
#THYROID	(20)	(49)	(50)
CYSTIC FOLLICLES	1 (5%)		1 (2%)
HYPERPLASIA, C-CELL	7 (35%)	15 (31%)	12 (24%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(50)	(50)
DILATATION/DUCTS	6 (30%)	2 (4%)	
*UTERUS	(20)	(50)	(49)
HEMORRHAGIC CYST		1 (2%)	
*CERVIX UTERI	(20)	(50)	(49)
POLYP			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
#UTERUS/ENDOMETRIUM	(20)	(50)	(49)
CYST, NOS	2 (10%)	1 (2%)	
HYPERPLASIA, CYSTIC		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(20)	(50)	(50)
HEMORRHAGE			1 (2%)
SPECIAL SENSE ORGANS			
*EYE	(20)	(50)	(50)
CATARACT		14 (28%)	6 (12%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED			1

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE ADMINISTERED SODIUM DIETHYLDITHIOCARBAMATE IN THE DIET

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED SODIUM DIETHYLDITHIOCARBAMATE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING	1		1
ANIMALS NECROPSIED	19	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	19	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(19)	(50)	(49)
ALOPECIA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(19)	(50)	(49)
HEMORRHAGE	1 (5%)		
HEMATOPOIETIC SYSTEM			
#SPLEEN	(19)	(50)	(49)
AMYLOIDOSIS		1 (2%)	
HYPERPLASIA, LYMPHOID		2 (4%)	
HEMATOPOIESIS	2 (11%)	6 (12%)	5 (10%)
#MESENTERIC L. NODE	(19)	(50)	(48)
HEMORRHAGE			1 (2%)
HYPERPLASIA, RETICULUM CELL	1 (5%)		
HYPERPLASIA, LYMPHOID		1 (2%)	1 (2%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(19)	(50)	(49)
CYST, NOS			1 (2%)
INFLAMMATION, NOS	1 (5%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
NECROSIS, FOCAL			1 (2%)
INFARCT, NOS			1 (2%)
AMYLOIDOSIS		1 (2%)	
CYTOPLASMIC VACUOLIZATION		6 (12%)	
BASOPHILIC CYTO CHANGE	1 (5%)	2 (4%)	2 (4%)
HYPERPLASIA, FOCAL		2 (4%)	
ANGIECTASIS		1 (2%)	
#PANCREAS	(19)	(50)	(49)
ATROPHY, NOS	1 (5%)		
#STOMACH	(18)	(50)	(48)
INFLAMMATION, FOCAL	1 (6%)		2 (4%)
#SMALL INTESTINE	(19)	(50)	(49)
HYPERPLASIA, LYMPHOID		2 (4%)	
URINARY SYSTEM			
#KIDNEY	(19)	(50)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (5%)		1 (2%)
INFLAMMATION, INTERSTITIAL		2 (4%)	
AMYLOIDOSIS		1 (2%)	
#KIDNEY/TUBULE	(19)	(50)	(49)
NECROSIS, NOS			1 (2%)
ENDOCRINE SYSTEM			
#THYROID	(19)	(49)	(48)
CYSTIC FOLLICLES		1 (2%)	
FOLLICULAR CYST, NOS		1 (2%)	2 (4%)
#PARATHYROID	(10)	(25)	(33)
CYST, NOS		1 (4%)	
#PANCREATIC ISLETS	(19)	(50)	(49)
HYPERPLASIA, NOS	2 (11%)	2 (4%)	
REPRODUCTIVE SYSTEM			
#PREPUTIAL GLAND	(19)	(50)	(49)
CYST, NOS			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
#BRAIN	(19)	(50)	(49)
MINERALIZATION	7 (37%)	17 (34%)	31 (63%)
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(19)	(50)	(49)
CYST, NOS	1 (5%)	3 (6%)	
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		3	4
ANIMAL MISSING/NO NECROPSY	1		1

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE ADMINISTERED SODIUM DIETHYLDITHIOCARBAMATE IN THE DIET

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	20	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	20	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	20	49	50
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(20)	(49)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR		1 (2%)	
METAPLASIA, OSSEOUS	1 (5%)		
HEMATOPOIETIC SYSTEM			
#SPLEEN	(20)	(48)	(50)
HEMORRHAGIC CYST		1 (2%)	
HYPERPLASIA, RETICULUM CELL	1 (5%)		1 (2%)
HYPERPLASIA, LYMPHOID		2 (4%)	
HEMATOPOIESIS	3 (15%)	5 (10%)	2 (4%)
#MANDIBULAR L. NODE	(19)	(46)	(49)
HYPERPLASIA, LYMPHOID		1 (2%)	
#MESENTERIC L. NODE	(19)	(46)	(49)
CYST, NOS	1 (5%)		
HYPERPLASIA, LYMPHOID		1 (2%)	2 (4%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(20)	(49)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR		2 (4%)	3 (6%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
NECROSIS, FOCAL	1 (5%)	1 (2%)	
CYTOPLASMIC VACUOLIZATION		1 (2%)	
BASOPHILIC CYTO CHANGE		1 (2%)	1 (2%)
ANGIECTASIS	2 (10%)		
#STOMACH	(20)	(49)	(48)
INFLAMMATION, FOCAL	1 (5%)	2 (4%)	4 (8%)
#SMALL INTESTINE	(20)	(49)	(50)
HYPERPLASIA, LYMPHOID			1 (2%)
URINARY SYSTEM			
#KIDNEY	(20)	(49)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR		2 (4%)	3 (6%)
#URINARY BLADDER	(20)	(48)	(49)
LYMPHOCYTIC INFLAMMATORY INFILTR	1 (5%)		1 (2%)
ENDOCRINE SYSTEM			
#ADRENAL	(20)	(49)	(50)
ATROPHY, NOS		1 (2%)	
#THYROID	(20)	(49)	(48)
CYSTIC FOLLICLES		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(20)	(49)	(50)
INFLAMMATION, GRANULOMATOUS			1 (2%)
#UTERUS	(20)	(49)	(49)
CYST, NOS		1 (2%)	
#UTERUS/ENDOMETRIUM	(20)	(49)	(49)
CYST, NOS	4 (20%)	23 (47%)	12 (24%)
#OVARY	(20)	(49)	(48)
CYST, NOS	2 (10%)	10 (20%)	5 (10%)
NERVOUS SYSTEM			
#BRAIN	(20)	(49)	(49)
MINERALIZATION	8 (40%)	16 (33%)	12 (24%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	MATCHED CONTROL	LOW DOSE	HIGH DOSE
HYDROCEPHALUS, NOS	1 (5%)		
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MESENTERY	(20)	(49)	(50)
GRANULOMA, NOS		1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(20)	(49)	(50)
LYMPHOCYTIC INFLAMMATORY INFILTR			1 (2%)
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	2	7	9
ANIMAL MISSING/NO NECROPSY		1	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX E

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN RATS ADMINISTERED SODIUM DIETHYLDITHIOCARBAMATE IN THE DIET

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Sodium Diethyldithiocarbamate in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma (b)	0/16 (0)	2/50 (4)	3/50 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.100	0.203
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	104	104
Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b)	2/16 (13)	4/50 (8)	5/50 (10)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.640	0.800
Lower Limit		0.105	0.152
Upper Limit		6.719	7.969
Weeks to First Observed Tumor	104	104	104

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Sodium Diethyldithiocarbamate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System:			
Leukemia (b)	4/16 (25)	13/50 (26)	14/50 (28)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.040	1.120
Lower Limit		0.395	0.433
Upper Limit		3.934	4.192
Weeks to First Observed Tumor	101	57	65
Pituitary: Adenoma, NOS (b)	5/16 (31)	7/50 (14)	6/48 (13)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.448	0.400
Lower Limit		0.151	0.125
Upper Limit		1.599	1.481
Weeks to First Observed Tumor	104	98	104

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Sodium Diethyldithiocarbamate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Adrenal: Cortical Carcinoma or Adenoma (b)	0/16 (0)	3/50 (6)	0/50 (0)
P Values (c,d)	N.S.	N.S.	--
Relative Risk (f)		Infinite	--
Lower Limit		0.203	--
Upper Limit		Infinite	--
Weeks to First Observed Tumor	--	104	--
Adrenal: Pheochromocytoma (b)	2/16 (13)	2/50 (4)	5/50 (10)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.320	0.800
Lower Limit		0.026	0.152
Upper Limit		4.203	7.969
Weeks to First Observed Tumor	104	104	90

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Sodium Diethyldithiocarbamate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: Follicular-cell Carcinoma or Adenoma (b)	0/15 (0)	5/50 (10)	3/49 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.403	0.196
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	104	103
Thyroid: C-cell Carcinoma or Adenoma (b)	3/15 (20)	10/50 (20)	3/49 (6)
P Values (c,d)	P = 0.047 (N)	N.S.	N.S.
Relative Risk (f)		1.000	0.306
Lower Limit		0.313	0.048
Upper Limit		5.192	2.120
Weeks to First Observed Tumor	104	102	104

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Sodium Diethyldithiocarbamate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pancreatic Islets: Islet-cell Adenoma (b)	3/16 (19)	2/49 (4)	1/48 (2)
P Values (c,d)	P = 0.027 (N)	N.S.	P = 0.045 (N)
Relative Risk (f)		0.218	0.111
Lower Limit		0.020	0.002
Upper Limit		1.773	1.296
Weeks to First Observed Tumor	104	102	104
Testis: Interstitial-cell Tumor (b)	14/16 (88)	42/50 (84)	45/50 (90)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.960	1.029
Lower Limit		0.819	0.880
Upper Limit		1.333	1.358
Weeks to First Observed Tumor	100	88	90

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats
Administered Sodium Diethyldithiocarbamate in the Diet (a)

(continued)

(a) Dosed groups received 1,250 or 2,500 ppm.

(b) Number of tumor-bearing animals/number of animals examined at site (percent).

(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.

(d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.

(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

(f) The 95% confidence interval of the relative risk between each dosed group and the control group.

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Sodium Diethyldithiocarbamate in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma (b)	2/20 (10)	3/50 (6)	4/50 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.600	0.800
Lower Limit		0.076	0.128
Upper Limit		6.860	8.436
Weeks to First Observed Tumor	104	104	104
Hematopoietic System: Leukemia (b)	1/20 (5)	5/50 (10)	2/50 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		2.000	0.800
Lower Limit		0.249	0.045
Upper Limit		92.596	46.273
Weeks to First Observed Tumor	104	101	89

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Sodium Diethyldithiocarbamate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Adenoma, NOS (b)	9/20 (45)	9/50 (18)	16/50 (32)
P Values (c,d)	N.S.	P = 0.023 (N)	N.S.
Departure from Linear Trend (e)	P = 0.019		
Relative Risk (f)		0.400	0.711
Lower Limit		0.176	0.375
Upper Limit		0.987	1.559
Weeks to First Observed Tumor	90	101	65
Thyroid: C-cell Carcinoma or Adenoma (b)	2/20 (10)	2/49 (4)	5/50 (10)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.408	1.000
Lower Limit		0.032	0.184
Upper Limit		5.381	10.007
Weeks to First Observed Tumor	104	104	89

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Sodium Diethyldithiocarbamate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Mammary Gland: Fibroadenoma (b)	3/20 (15)	3/50 (6)	0/50 (0)
P Values (c,d)	P = 0.010 (N)	N.S.	P = 0.021 (N)
Relative Risk (f)		0.400	0.000
Lower Limit		0.060	0.000
Upper Limit		2.802	0.659
Weeks to First Observed Tumor	98	101	--
Uterus: Endometrial Stromal Polyp (b)	3/20 (15)	7/50 (14)	10/49 (20)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.933	1.361
Lower Limit		0.245	0.406
Upper Limit		5.215	7.138
Weeks to First Observed Tumor	101	104	104

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Sodium Diethyldithiocarbamate in the Diet (a)

(continued)

(a) Dosed groups received 1,250 or 2,500 ppm.

(b) Number of tumor-bearing animals/number of animals examined at site (percent).

(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.

(d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.

(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

(f) The 95% confidence interval of the relative risk between each dosed group and the control group.

APPENDIX F

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN MICE ADMINISTERED SODIUM DIETHYLDITHIOCARBAMATE IN THE DIET

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Sodium Diethyldithiocarbamate in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma (b)	5/19 (26)	10/50 (20)	8/49 (16)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.760	0.620
Lower Limit		0.284	0.213
Upper Limit		2.547	2.172
Weeks to First Observed Tumor	105	100	103
Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b)	6/19 (32)	14/50 (28)	14/49 (29)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.887	0.905
Lower Limit		0.392	0.401
Upper Limit		2.480	2.526
Weeks to First Observed Tumor	105	100	70

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Sodium Diethyldithiocarbamate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System:			
Lymphoma or Leukemia (b)	2/19 (11)	12/50 (24)	10/49 (20)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		2.280	1.939
Lower Limit		0.587	0.476
Upper Limit		19.837	17.231
Weeks to First Observed Tumor	105	78	21
All Sites: Hemangiosarcoma (b)	1/19 (5)	3/50 (6)	1/49 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.140	0.388
Lower Limit		0.101	0.005
Upper Limit		58.635	29.845
Weeks to First Observed Tumor	85	103	108

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Sodium Diethyldithiocarbamate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma (b)	5/19 (26)	9/50 (18)	8/49 (16)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.684	0.620
Lower Limit		0.246	0.213
Upper Limit		2.339	2.172
Weeks to First Observed Tumor	105	107	102
Liver: Hepatocellular Carcinoma or Adenoma (b)	7/19 (37)	11/50 (22)	11/49 (22)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.597	0.609
Lower Limit		0.262	0.267
Upper Limit		1.592	1.622
Weeks to First Observed Tumor	105	107	102

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Sodium Diethyldithiocarbamate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Mesentery: Lipoma (b)	2/19 (11)	2/50 (4)	1/49 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.380	0.194
Lower Limit		0.030	0.003
Upper Limit		5.009	3.563
Weeks to First Observed Tumor	109	108	108

(a) Dosed groups received 500 or 4,000 ppm.

(b) Number of tumor-bearing animals/number of animals examined at site (percent).

(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.

(d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.

(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

(f) The 95% confidence interval of the relative risk between each dosed group and the control group.

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Sodium Diethyldithiocarbamate in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma (b)	0/20 (0)	3/49 (6)	4/50 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.255	0.386
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	109	108
Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b)	0/20 (0)	7/49 (14)	8/50 (16)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.826	0.952
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	109	108

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Sodium Diethyldithiocarbamate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System:			
Lymphoma (b)	9/20 (45)	7/49 (14)	13/50 (26)
P Values (c,d)	N.S.	P = 0.009 (N)	N.S.
Departure from Linear Trend (e)	P = 0.007		
Relative Risk (f)		0.317	0.578
Lower Limit		0.125	0.289
Upper Limit		0.835	1.316
Weeks to First Observed Tumor	98	99	89
Pituitary: Carcinoma, NOS, or			
Adenoma, NOS (b)	2/19 (11)	2/47 (4)	0/49 (0)
P Values (c,d)	P = 0.037 (N)	N.S.	N.S.
Relative Risk (f)		0.404	0.000
Lower Limit		0.032	0.000
Upper Limit		5.318	1.303
Weeks to First Observed Tumor	109	104	--

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Sodium Diethyldithiocarbamate in the Diet (a)

(continued)

(a) Dosed groups received 500 or 4,000 ppm.

(b) Number of tumor-bearing animals/number of animals examined at site (percent).

(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.

(d) A negative trend (N) indicates a lower incidence in a dosed group than in a control group.

(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

(f) The 95% confidence interval of the relative risk between each dosed group and the control group.

Review of the Bioassay of Sodium Diethyldithiocarbamate* for Carcinogenicity
by the Data Evaluation/Risk Assessment Subgroup
of the Clearinghouse on Environmental Carcinogens

December 13, 1978

The Clearinghouse on Environmental Carcinogens was established in May, 1976, in compliance with DHEW Committee Regulations and the Provisions of the Federal Advisory Committee Act. The purpose of the Clearinghouse is to advise the Director of the National Cancer Institute on the Institute's bioassay program to identify and evaluate chemical carcinogens in the environment to which humans may be exposed. The members of the Clearinghouse have been drawn from academia, industry, organized labor, public interest groups, and State health officials. Members have been selected on the basis of their experience in carcinogenesis or related fields and, collectively, provide expertise in chemistry, biochemistry, biostatistics, toxicology, pathology, and epidemiology. Representatives of various Governmental agencies participate as ad hoc members. The Data Evaluation/Risk Assessment Subgroup of the Clearinghouse is charged with the responsibility of providing a peer review of reports prepared on NCI-sponsored bioassays of chemicals studied for carcinogenicity. It is in this context that the below critique is given on the bioassay of Sodium Diethyldithiocarbamate.

The reviewer for the report on the bioasay of Sodium Diethyldithiocarbamate agreed with the conclusion that the compound was not carcinogenic under the conditions of test. After a brief description of the experimental design, he said that the only shortcoming of the study was the inadequate size of the matched control groups. Based on the results of the study, he said that there was no evidence that Sodium Diethyldithiocarbamate would pose a carcinogenic risk to human beings. The reviewer moved that the report on the bioassay of the compound be accepted as written. The motion was seconded and approved without objection.

Clearinghouse Members Present:

Arnold L. Brown (Chairman), University of Wisconsin Medical School
Joseph Highland, Environmental Defense Fund
William Lijinsky, Frederick Cancer Research Center
Henry Pitot, University of Wisconsin Medical Center
Verne A. Ray, Pfizer Medical Research Laboratory
Verald K. Rowe, Dow Chemical USA
Michael Shimkin, University of California at San Diego

Louise Strong, University of Texas Health Sciences Center
Kenneth Wilcox, Michigan State Health Department

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* Subsequent to this review, changes may have been made in the bioassay report either as a result of the review or other reasons. Thus, certain comments and criticisms reflected in the review may no longer be appropriate.

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